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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|-----------------|-------------|----------------------|---------------------|------------------|
| 09/592,007 | 06/12/2000 | Francis Tufaro | 08582/009002 | 4193 |

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02/26/2003

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| EXAMINER |
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SCHULTZ, JAMES

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| ART UNIT | PAPER NUMBER |
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1635

DATE MAILED: 02/26/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

File

Office Action Summary

Application No.

09/592,007

Applicant(s)

TUFARO ET AL.

Examiner

J. Douglas Schultz

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 23 December 2002.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-5, 7-10, 13, 15-22 and 24-27 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-5, 7-10, 13, 15-22 and 24-27 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892) ✓
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____

- 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other:

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DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on December 23, 2003 has been entered.

Response to Arguments

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1-5, 7-10, 13, 15-22, and 24-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hodgson et al. in view of Dyer et al., Marasco et al., and Mislick et al., for the same reasons of record as set forth in the Office action mailed September 25, 2001.

The invention of the above claims is drawn to a method for introducing a virus into a cell *in vivo* comprising contacting said cell with a virus and a charged compound, wherein said compound may be a charged polysaccharide, a polylysine, an acyclodextrin, a diethylaminoethane, or a polyethylene glycol, wherein said charged polysaccharide may be dextran sulfate, or wherein the virus is of a specific type or species, or wherein the virus carries a therapeutic product, or wherein the cell is in a human or may be a cancer cell, muscle cell, or wherein the human has a condition to be treated by the therapeutic gene of the virus.

Applicants traverse the rejection above on the grounds that the examiner did not provide a sufficient basis for combining the references. Applicants particularly traverse the combination of Dyer, which was relied upon for teaching that glycosaminoglycans (GAGs) can assist viral transfection, with the remaining references, such that one of skill in the art would arrive at the presently claimed invention. Applicants argue that in addition to the failure to provide motivation to combine the references, that Dyer actually teaches away from the present invention whereby viral specific entry into cells is enhanced *in vivo* by the presence of a charged compound, because Applicants argue that there is no indication that Dyer's method would have a positive effect on transfection *in vivo*, and because statements discussed below appear to support Applicants contention that Dyer actually teaches away from the present methods. Applicants emphasize that Dyer's use of a cell line lacking endogenously produced GAGs is the only reason that the charged compound of Dyer (dextran sulfate, DS) was found to enhance viral-specific cellular transfection, and that statements presented in this paper point away from the successful practice of Dyer's method in the whole animal *in vivo*.

These arguments have been considered but are not persuasive. In response to applicant's argument that there is no suggestion to combine the references, particularly in regards to Dyer, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992).

In this case, in response to the allegation that there is no motivation in particular to combine the methods of the instant references with Dyer, it is pointed out that Hodgson was relied upon in part for teaching a method of transfecting cells using viral particles in combination with a charged compound, and that Hodgson teaches that this method could be used *in vivo* to enhance gene therapy. Because one of ordinary skill in the art is motivated to enhance gene therapy, as underscored throughout the introduction of Hodgson et al., and because Dyer et al. teach both a method of enhancing transfection of HSV-1 using DS, and that HSV-1 is capable of infecting a variety of cell types in different animals, one would have been motivated to combine the methods of the references *in vivo*; thus one of ordinary skill in the art would have arrived at the invention as presently claimed.

Applicant has also argued that the teachings of Dyer et al. actually teach away from the present invention, and have supplied comments to substantiate this claim. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

However, regarding the argument that Dyer et al. teaches away from the motivation to combine as described above, it is pointed out that all of Applicants' statements supplied from the text of Dyer do not concretely teach away from the motivation above, but merely suggest several potential mechanisms, of which some may have elements that complicate *in vivo* function. However, these potential complications do not amount to a teaching away from the present

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invention, because said statements are taken out of context and do not support the conclusions drawn by Applicant. For example, Applicants' cite the statement of Dyer that DS is not covalently linked to the host cell, which therefore is likely to severely compromise its ability to stabilize HSV-1 virions that collide with the cell surface; in Applicants' opinion, this statement provides "a very firm basis for the conclusion that *in vivo*, in the context of the naturally occurring glycosaminoglycans, exogenously administered dextran sulfate may not have an effect". However, this assertion fails to account for the fact that the DS used by Dyer also wasn't covalently attached, yet still was clearly able to enhance viral-specific entry in this study; this speculation by the authors sought to provide a potential reason as to why DS doesn't completely restore wild type levels of infection in GAG-minus cells, and does not provide any reason to doubt that adding DS to GAG expressing cells *in vivo* might have some additive effect. It is thus not clear how this statement would deter one of ordinary skill in the art from using DS to enhance viral-specific cell entry.

Applicants' further cite Dyer's statement that the effects of DS may not be detectable in cells that display heparan sulfate, and conclude that therefore, it may be that *in vivo*, DS has no effect on viral transfection. However, it is pointed out that the context in which this statement appears is in the discussion of why Dyer's results are novel. This statement is not elaborated upon by the author, and follows a much longer statement whereby a mechanism is set forth that DS may be bound by scavenger receptors (that are themselves expressed on several cell types *in vivo*) that renders the cell more susceptible to HSV-1 infection, a situation that fairly suggests that the present invention may work *in vivo*.

Applicants' after final amendment entered September 23, 2002, cited a statement from Dyer that DS normally inhibits infection of cells by enveloped viruses, in support of Applicants' contention that Dyer teaches away from the present invention. This statement was rebutted in the advisory action mailed October 16, 2002, on the grounds that it is precisely this context that made Dyer's findings of note. Applicants disagree, saying that "Dyer did not contradict what was known to happen with normal cells that contain GAGs (i.e., that DS normally inhibits infection of cells by enveloped viruses), but rather contrasted what they observed in mutant cells that lack GAG's with what happens in normal cells." It is unclear how this statement has been interpreted as teaching away from the present invention, particularly in light of the fact that Dyer clearly states his surprise when comparing his results to what is known to happen in normal cells. Because Dyer's surprise is evidently drawn to the contrast of results from his GAG-minus cells to those that express GAGs, it is apparent that Dyer et al. are of the opinion that such a comparison has at least some validity; if such a comparison was not appropriate, it would be hard to imagine the authors stating their surprise. Dyer then further discuss in some detail a mechanism that raises the possibility of *in vivo* function, said mechanism containing no mention of possible interference by endogenous GAGs.

Finally, in contrast to Applicants' contention that Dyer teaches away from the present invention, the introduction of Dyer contains a statement that there appears to be additional non-GAG receptors that facilitate a productive infection; this suggests that an alternate non-GAG pathway may exist to be exploited in enhancing viral-specific entry. It would appear that Applicants arguments, which depend solely on GAG inhibition of DS-mediated enhancement fo

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viral entry, are undermined, since from the authors' statements we can infer that GAGs are not the only determinant of viral entry. When the paper is read as a whole and the statements provided Applicant are put in their proper context, it becomes apparent that Dyer et al. does not clearly teach away from motivating one of ordinary skill in the art in attempting the use of DS to enhance viral specific cell entry *in vivo*.

This is an RCE of applicant's earlier Application No. 09/592,007. All claims are drawn to the same invention claimed in the earlier application and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the earlier application. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action in this case. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no, however, event will the statutory period for reply expire later than **SIX MONTHS** from the mailing date of this final action.


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Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. Douglas Schultz whose telephone number is 703-308-9355. The examiner can normally be reached on 8:00-4:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on 703-308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

James Douglas Schultz, PhD
February 20, 2003


ANDREW WANG
SUPERVISORY PATENT EXAMINER
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